GEA

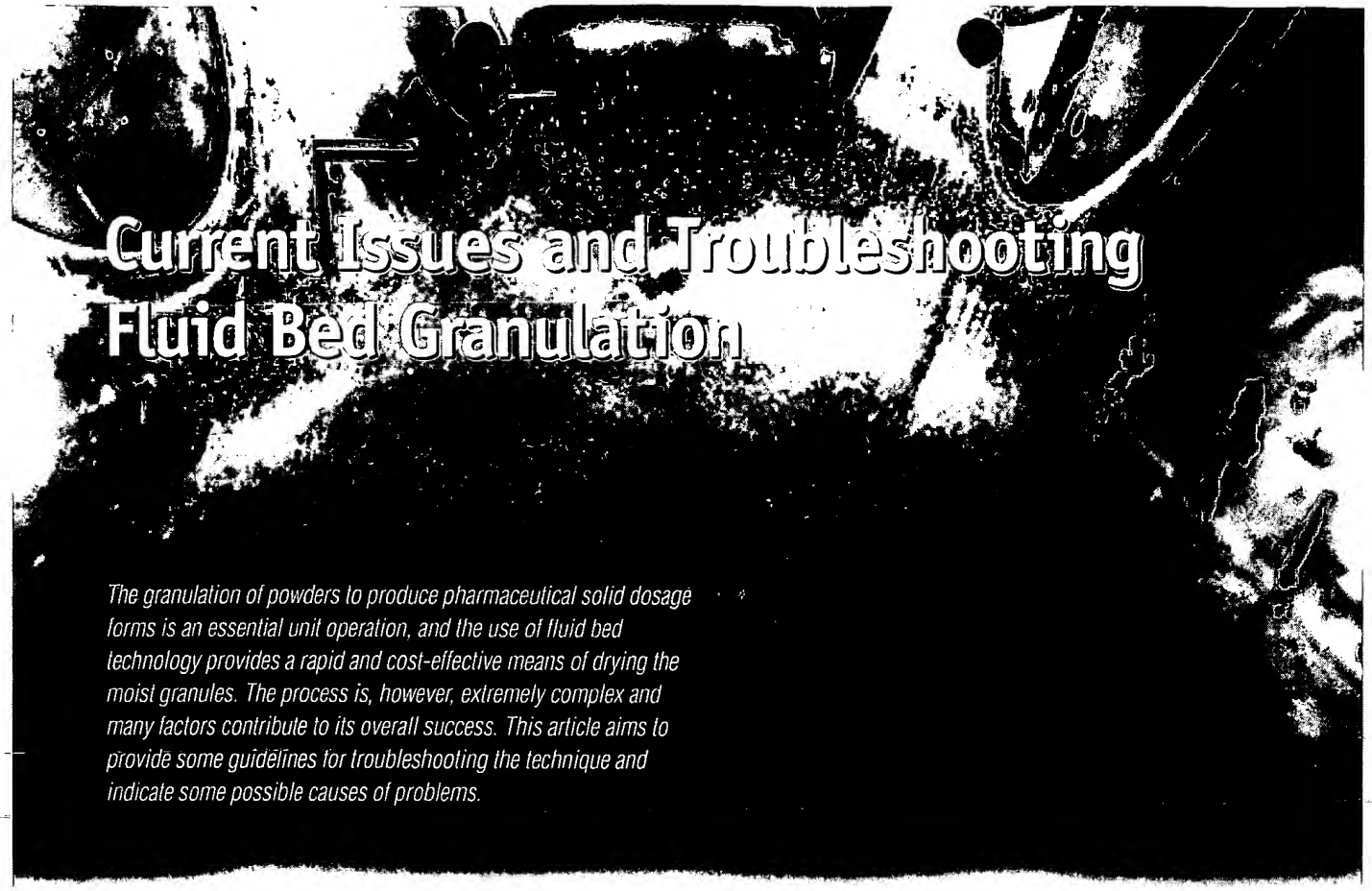
Niro Pharma Systems

Current Issues and Troubleshooting Fluid Bed Granulation

Article reprinted from

Pharmaceutical Technology EUROPE

EXHIBIT B



Current Issues and Troubleshooting Fluid Bed Granulation

The granulation of powders to produce pharmaceutical solid dosage forms is an essential unit operation, and the use of fluid bed technology provides a rapid and cost-effective means of drying the moist granules. The process is, however, extremely complex and many factors contribute to its overall success. This article aims to provide some guidelines for troubleshooting the technique and indicate some possible causes of problems.

Image courtesy of Heinen AG, Germany. Artwork by Peter Bartley.

Granulation may be considered as a size-enlargement process, during which primary particles are formed into larger, physically strong agglomerates wherein the primary particles can still be identified. The main objectives of granulation are to improve the flow properties and compression characteristics of the mix, and to prevent segregation of the constituents. Table I lists the different types of granulation processes used.

The basic wet-granulated granule may be visualized as two particles connected by a liquid bridge that serves to hold the particles together in two ways — by surface tension at the air-liquid interface and by hydrostatic suction. A fluid bed processor is a system of unit operations involving the heating of process air, directing it through the material to be processed, and then removing the same air (usually laden with moisture) from the unit, void of the product (Figure 1). A fluidized bed is a bed of solid particles with a stream of air passing upward through the particles at a rate sufficient to set them in motion. As the air travels through the particle bed, it imparts unique properties to the bed, similar to those of a liquid. It is possible to propagate wave motion within the bed, which creates the potential for increased mixing. Fluidized bed granulation is a process by which granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. To achieve a good granulation, particles must be uniformly mixed and liquid bridges between the particles must be strong and easy to dry.

The granulation process in the fluid bed (Figure 2), requires a binary nozzle, a solution delivery system and compressed air to atomize the liquid binder. When the binder liquid is sprayed on to a fluidized bed, relatively loose and very porous granules are formed. During spraying, a portion of the liquid is immediately lost to evaporation — thus, the system has little tendency to pass beyond the liquid bridge phase. The particle size of the resulting granules can be controlled by adjusting the quantity and droplet size of the binder.

The variables: equipment and process

To troubleshoot any process, one needs to understand the product, the equipment being used and the process being performed. The knowledge of the inter-relationship between these variables is essential to solving related problems. The pharmaceutical industry and the suppliers of fluid beds have demanded and implemented improvements in the relevant hardware and process controls to minimize granulation problems. This co-operation was further inspired by the insistence of the regulatory authorities, in various countries, for the validation of the equipment and process before commercialization of a pharmaceutical product.

Factors affecting the fluid bed granulation process can be divided into three broad categories — formulation related variables, equipment related variables and process related variables. As the topic of formulation related variables is outside the scope of this article, only the equipment and process related variables will be highlighted. These include:

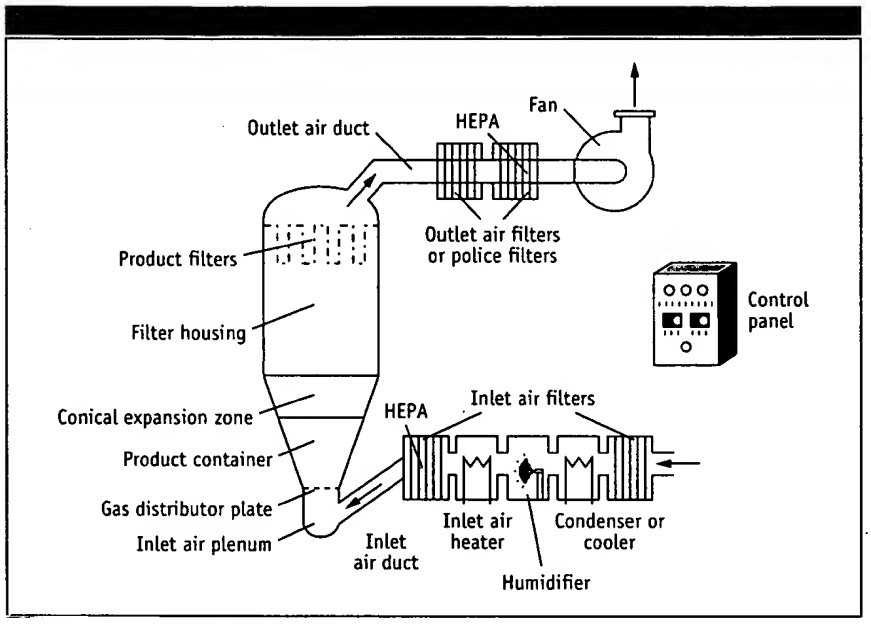


Figure 1: *The fluid bed processing system.*

1. Equipment related variables
- design
- scalability
- air distributor plate
- pressure drop
- filter shaking.

2. Process related variables
- process inlet air temperature
- nozzle atomization air pressure and volume
- fluidization air velocity and volume
- liquid spray rate
- nozzle: position and number of spray heads
- product and exhaust air temperature
- filter porosity and cleaning frequency.

Common problems in fluid bed granulation

For brevity, and to provide a readily accessible source of information, a list of the six most common problems encountered during granulation is provided. Beneath each subheading are possible causes of the problem, that should be examined and, if necessary, adjusted, to improve the performance of the process.

1. Excessively coarse granules
- inlet air temperature too low
- high spray rate
- pump calibration problems
- nozzle position too low
- atomization air is not on and binder does not atomize
- change in raw material particle to a coarser size
- nozzle leakage.

2. Excessive fines
- inlet air temperature is too high
- binder spray rate is too low
- insufficient quantity of binder
- high fluidization velocity or air flow
- weak binder
- change in particle size to a finer one
- high atomization air pressure, finer binder droplets.

3. Final moisture inconsistency
- inadequate process development-drying curve
- improper fluidization
- temperature probe out of calibration.

4. Poor fluidization
- too much product in the product container
- incorrect air distributor plate
- processor fan does not have adequate pressure drop
- air distributor not cleaned properly
- exhaust filter porosity too small
- exhaust filter is blocked.

5. Low yield
- wrong porosity exhaust filter
- air distributor with coarser screen opening
- filter bag with a tear in it
- filter bag not shaken at the end of the process
- material sticks to the walls of the expansion chamber as a result of static charge.

6. Finished product non-uniformity
- insufficient filter shaking
- product homogeneity before granulation not adequate
- lumpy raw materials
- spraying time insufficient.

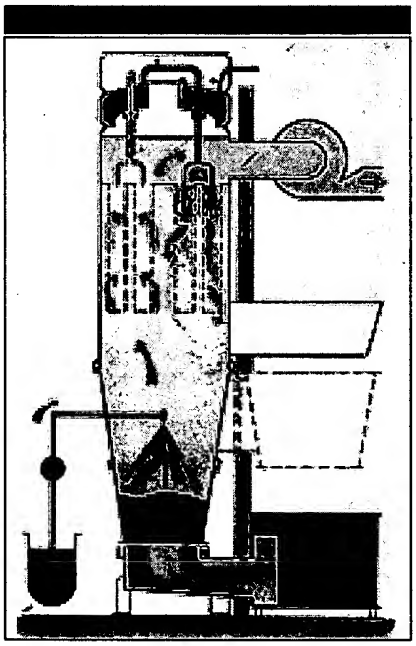


Figure 2: *A fluid bed spray granulator.*

Table I: *Various granulation methods.*

Granulation process	Methodology
Dry processes	Slugging Roller compaction
Wet processes	Pan granulation Spray drying High shear granulation (wet massing) Extrusion/spheronization Fluid bed granulation

Current issues and recent advances

The current state of the technology provides the tools to troubleshoot the fluid bed granulation process. Some examples are given below:

Ten bar design (Figure 3)

Fluid bed processing involves fine dust and a large amount of processing air, which, triggered by a static charge, can cause an explosion. Such an explosion creates a momentary over-pressure in the processor. A typical design, that was available until the late 1970s, was only capable of withstanding a two bar over-pressure. However, this type of unit required a relief duct to vent the pressure front in the event of an explosion. The processor had to protrude through the roof or be installed near the outside wall of the facility to minimize the length of the pressure relief duct. The processor also required doors equipped with gaskets, posing cleaning problems. The introduction of the 10-bar design eliminated the need for pressure

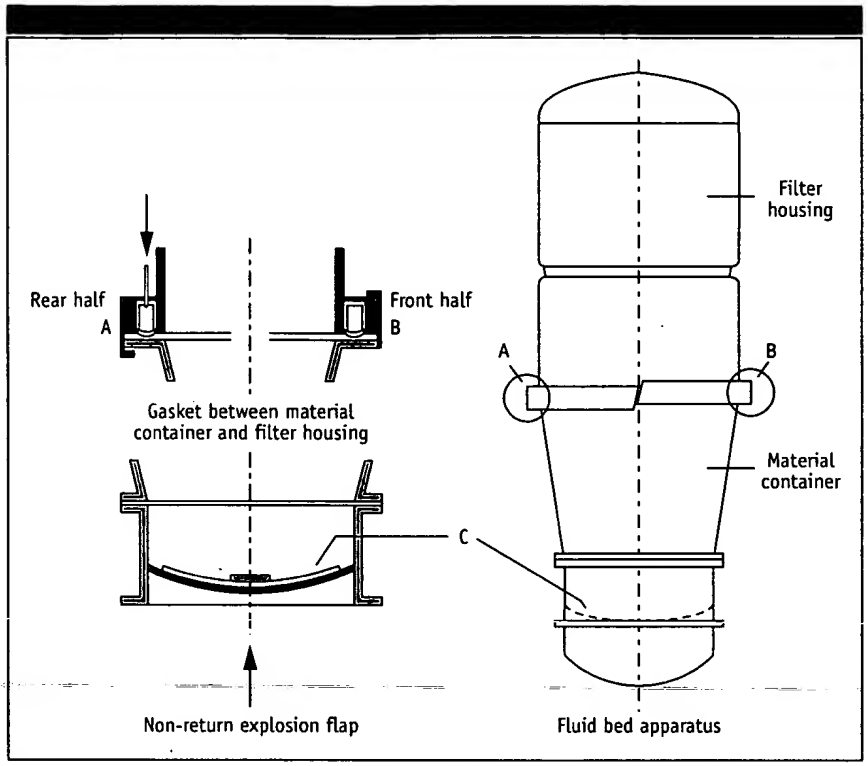


Figure 3: *A ten bar fluid bed unit.*

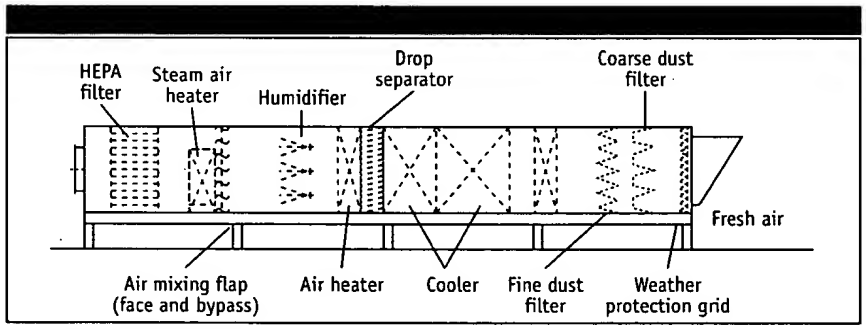


Figure 4: *Air handling unit.*

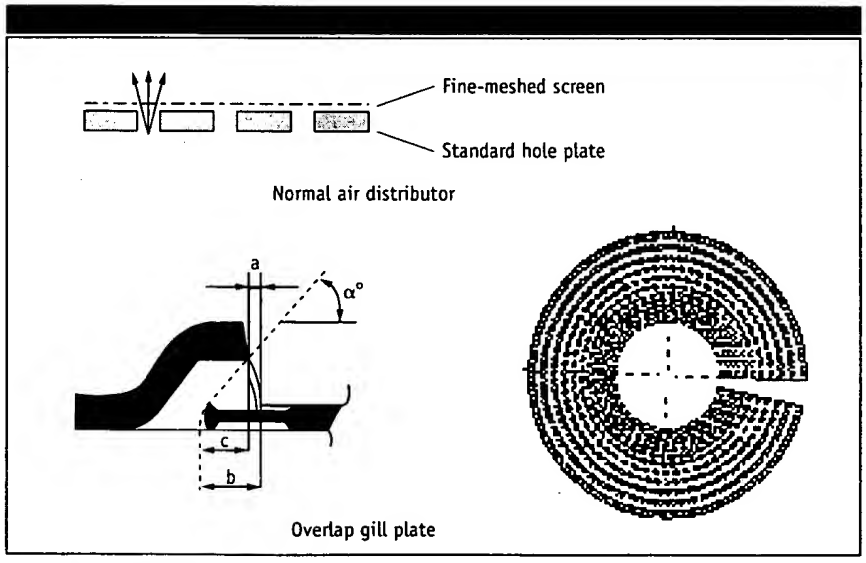


Figure 5: *Air distributor.*

relief ducts and the related cleaning problems. Today, a production-size fluid bed granulator with a 10 bar-pressure shock resistance can be procured.

Air handling unit (Figure 4)

A typical air preparation system includes sections for air filtering, air heating, air cooling and humidity removal. For a fluid bed processor used in pharmaceutical manufacturing, the process air is drawn from the outside of the building. The conditioning of this air to a constant humidity and dew point is essential. The drying capacity of the air depends on its temperature, humidity and volume. Because of the globalization of the pharmaceutical industry, fluid bed granulation processes must be able to operate in any environment at any time of the year. This has led to the current design of the air-handling unit for the fluid bed processor.

Air distributor (Figure 5)

The process air brought into the fluid bed processor must be evenly distributed to obtain uniform fluidization of the product being granulated. The formerly used perforated stainless steel screens, along with fine mesh screens, posed problems if a tear occurred in the screen — or inadequate cleaning occurred, resulting in the loss of product or fluidization problems.

In 1990, a new design of the air distributor, called the 'overlap gill plate' was introduced.[1] The overlap gill plate has the same capability of distributing air as the previously used design but, unlike the sandwiched type air distributor, this new air distributor is easier to clean, sturdy and can be welded in place to form a clean-in-place (CIP) unit. This type of air distributor also facilitates side product discharge, which was not possible with the sandwich type air distributor.

Process filters (Figure 6)

Process filters retain the product in the processor. The early cloth filter design has changed from a single-stroke shake to the split-shaker design, to provide continuous fluidization. To prevent cross-contamination of the products, industry uses dedicated filter bags for each product. The washing of these bags is cumbersome. The bags are made up of poly(propylene), nylon or poly(ester) and, because the bags are generally hand sewn and have numerous seams, they can tear upon repeated use. If the tear happens during processing, product can be lost. Moreover, filter bag handling and cleaning poses a problem of operator safety when a potent compound is processed. Cartridge filters were introduced to partially address these concerns.[2] The

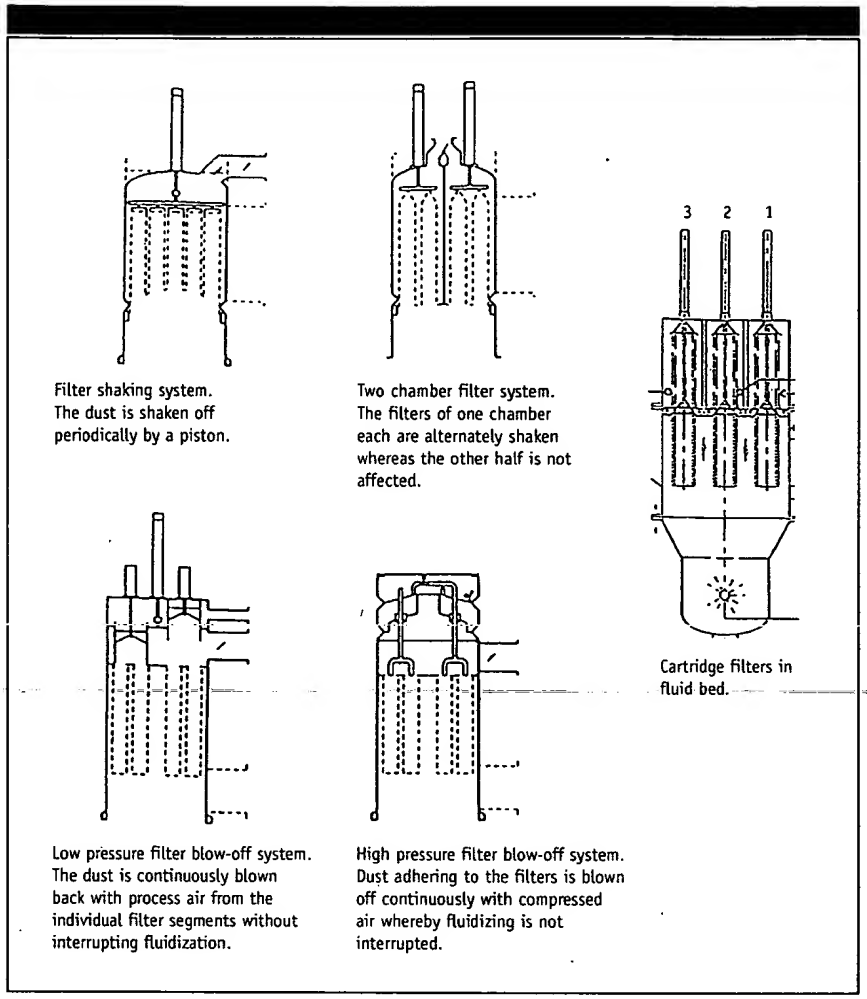


Figure 6: *Various process filters and cleaning mechanisms.*

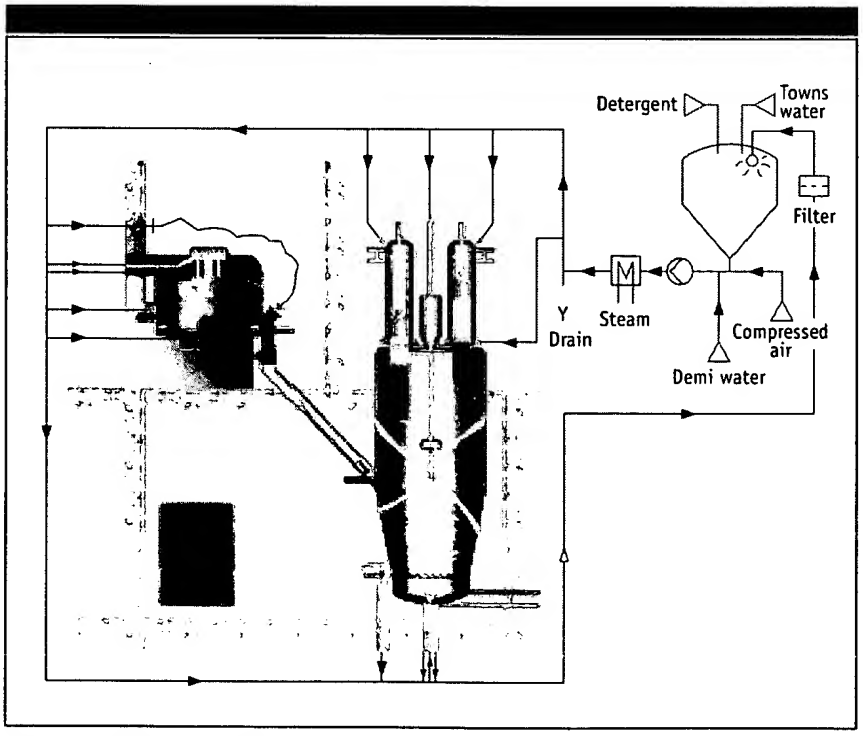


Figure 7: *Clean-in-place design.*

earlier cartridges used a Gore-Tex laminated poly(ester) felt material, which was not suitable for a CIP system. Potent compounds generally require a CIP system. A pleated cartridge made of three layers of woven stainless steel was introduced in 1991. This was the first time that cleaning-in-place of fluid bed processors became a possibility.

CIP design (Figure 7)

Formerly, to clean fluid bed processing equipment, the filter bags and the air distributor, along with the sandwiched construction had to be removed from the unit and disassembled. The cleaning process required 8–10 hours, and the assurance of cleaning was sometimes operator-dependent. A true CIP for the fluid bed was achieved in 1993.[3] This was accomplished as a result of the introduction of the overlap gill air distributor and the stainless steel cartridge filters. Because the CIP system can be automated, cleaning can be performed without the involvement of the operator. This automation makes it possible to validate the cleaning system. By providing a tank washer for the processor, strategically placed cleaning nozzles and a cartridge cleaning system, the fluid bed can be cleaned-in-place. The unique cleaning system involves cartridges that can be raised and lowered during the cleaning cycles, a spray nozzle at the top of the cartridge and annular nozzles around the cartridge tower base. The pleats of the cartridge get cleaned as the cartridges are moved up and down and the force of the spray rotates the cartridges. At the same time, the nozzle at the top of the cartridge tower sprays liquid through the filter media and back-flushes the cartridge. The lower plenum and overlap gill air distributor are cleaned by a nozzle placed in the lower plenum. The cleaning regimen is determined in the early stages of cleaning method development and programmed to provide consistency.

Other advances

End point detection. The end point of a fluid bed drying or granulating process has customarily been determined by monitoring the temperature of the exhaust gas stream. The reproducibility of the process is determined by a combination of bed temperature, exhaust air temperature and drying time. A near infrared moisture measurement technology is currently being evaluated to measure product moisture directly during processing.

Automation and controls. Fluid bed processing requires accurate and reliable control of all the process parameters. Earlier designs of

process control systems used pneumatic controls, which provided safe operation in hazardous areas but relied on operator actions to achieve repeatable product quality and data acquisition. Current designs use programmable logic controllers (PLCs) and personal computers to achieve sophisticated control and data acquisition.

Conclusion

The fluid bed granulation process is an integral part of solid dosage manufacturing in the pharmaceutical industry. Significant progress has been made to address typical fluid bed granulation problems — such as control of particle size, bulk density, process uniformity, in-process controls, fluidization abnormalities, filter cleaning and validatable control systems — by the constant innovation by the supplier of these technologies and the requirements imposed by the regulatory authorities. Fluid bed granulation troubleshooting can be successfully addressed by knowing the equipment and process variables. By implementing the improvements in new technologies, fluid bed granulation will fulfil industry and regulatory expectations.

References

1. US Patent 5,392,531 (1991), European Patent 0507038A1 (1991) and International Patent PCT/DK92/00102 (1992).
2. Japanese Patent application 61-259696 (1986) and 62-44574 (1987).
3. Swiss Patent 0176/93 (1993), US Patent 5,444,892 (1995) and European Patent 0572356A1 (1993).

Reprinted from

Pharmaceutical Technology
EUROPE

©May 1998 issue.
Reprint Publication Number 00496

AN ADVANSTAR PUBLICATION